REMARKS

The present response is submitted in reply to the Office Action issued on May 29, 2008. Claims 1-10 are pending in this application, all of which have been rejected. By the present response, claims 1 and 3 have been amended. Claims 6 and 9 have been canceled. No new matter has been added. Reconsideration is respectfully requested in light of the following remarks.

Claim Objections

The Examiner has objected to claims 6 and 9 as being substantial duplicates of claim 1. In particular, the Examiner notes that the claims are drawn to the same product notwithstanding any intended use.

Both of these claims have been cancelled. Therefore, the objections are no longer germane. Withdrawal of the objections is appropriate.

Rejection of claims 1-10 under 35 U.S.C. 112, first and/or second paragraphs

Claim 9 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner states that claim 9 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner states that the claims contain the phrase "or medicament" which is not described in the specification in any manner, but rather the specification only provides description for a pharmaceutical composition.

Claim 9 has been cancelled, as noted above. Therefore, the rejection is no longer germane as it pertains to claim 9. Withdrawal of the rejection is appropriate.

Claims 1-10 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. In particular, the Examiner states that it is not clear what is meant by the phrase "the residue of an amino acid."

It is submitted that the aforementioned phrase has been clarified throughout the claims, as set forth above in the amended claims. Therefore, withdrawal of the rejection is appropriate.

Rejection of claims 1-10 under 35 U.S.C. 103(a)

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,169,804 (Ascher, et al.) and/or U.S. Patent No. RE39,128 E (Berry, et al.). In particular, the Examiner argues that Ascher, et al. and Berry, et al. teach antibacterial compounds and compositions corresponding to those recited in the present claims, and refers to column 1, line 1 through column 2, line 34 of Ascher, et al. and column 2, lines 2-52, column 3, lines 5-10 and Examples 10, 15 and 37 of Berry, et al. The Examiner further argues that while the alkyls on the corresponding R_5 substituent may differ in number, such differences in closely structured related compounds would have been obvious to one of ordinary skill in the art as the resulting products would not have been unexpected.

The Applicants respectfully submit that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or

motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitation. The Applicants respectfully submit that one skilled in the art would have no suggestion or motivation to modify and/or combine the aforementioned references in order to arrive at the presently claimed invention. Additionally, even if one skilled in the art were to consider the teachings of the cited prior art alone, or in combination, each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered either alone or in combination. In addition, prior art must be considered in its entirety, i.e., as a whole (emphasis provided), including portions that would lead away from the claimed invention (M.P.E.P. §2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220, USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)), the proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference (M.P.E.P. §2143.01), and Examiner's conclusion of obviousness may not be based on improper hindsight (M.P.E.P. §2145(X)(A)).

The Applicants respectfully traverse this rejection and respectfully submit that this rejection is in error and should not be maintained. The Applicants have enclosed herewith *in vitro* and *in vivo* data (i.e., "screening") of (1) compounds of the present invention (i.e., WO 2004011431, which corresponds to and is the equivalent of the present application), (2) a similar compound of Ascher, et al. '804 and (3) a similar compound of Berry, et al. '128, which are

elaborated upon in the attached "Materials and Methods."

In view of the attached data, it is respectfully submitted that the data set forth the superiority of the compounds of the present invention when compared with data obtained from compounds of Ascher, et al. '804 and Berry, et al. '128. In particular, it is submitted that the overall results of the data obtained from Examples 3 and 7 of the present application demonstrate excellent *in vitro* activity. Moreover, the aforementioned examples show excellent *in vivo* activities (e.g., ED_{50} = 8.72 mg/kg for Example 3 and 16.2 mg/kg for Example 7) as compared to the values from the cited prior art (e.g., ED_{50} = 8.83 mg/kg for Ascher, et al. '804 and 26.71 mg/kg for Berry, et al.).

It is further submitted that a comparison of the data of the most prominent example (i.e., retapamulin of Examples 50 and 58) from Berry, et al. with the data of examples of the present invention clearly set forth the improved *in vivo* activity of compounds of Examples 3 and 7 of the present invention. The improved *in vivo* efficacy is also shown by a comparison with the data of the compound of Example 1 of Ascher, et al. '804. It is submitted that these results clearly indicate improved *in vivo* activity of a compound of the present invention.

It is also submitted by the Applicants that one of the most prominent toxicities of pleuromutilins is liver toxicity. The *in vitro* hepatoxicity assay is able to indicate the hepatoxicity potential of the corresponding pleuromutilin derivative. In the *in vitro* hepatoxicity, the compounds of Example 3 (IC_{50} = 160 μg/ml) and Example 7 (IC_{50} = 131 μg/ml) of the present invention compared to Example 1 of Ascher, et al. (IC_{50} = 63 μg/ml) show remarkable higher IC_{50} values and therefore have a definitively lower potential for *in vivo* liver toxicity.

In summary, it is submitted that the compounds of Examples 3 and 7 of the

present invention have improved *in vivo* activity compared to the compounds of Examples 50 and 58 in Berry, et al. and liver toxicity is decreased compared with the compound of Example 1 of Ascher, et al. Improved efficacy of the compounds of the present invention as shown above could not be expected from either Ascher, et al. or Berry, et al., or even from a combination of the teachings of Ascher, et al. and Berry, et al., and therefore one skilled in the art would lack motivation to refer to and/or modify the teachings of the cited prior art in order to arrive at the presently claimed invention. Withdrawal of this rejection is strongly requested.

Conclusion

In light of the foregoing claims and arguments, it is believed that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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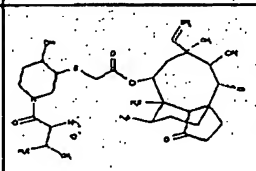
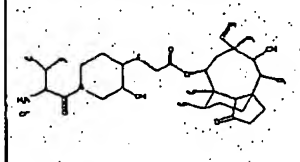
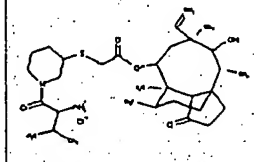
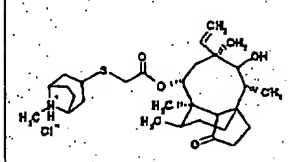
Example			3 in WO04011431	7 in WO04011431
				
In vitro				
Species		**Strain**	VBV 392	VBV 363
Staphylococcus aureus	ATCC 10390	B6	0.2	0.05
Staphylococcus aureus	ATCC 29213	B7	0.2	0.1
Staphylococcus aureus	ATCC 29506	B8	0.2	0.1
Staphylococcus aureus	ATCC 49951	B9	0.1	0.05
Staphylococcus aureus	ATCC 9144	B10	0.1	0.05
In vitro Hepatotoxicity human Hepatocytes	**IC50 [µg/ml]**		**160**	**131**
In vivo				
***In vivo* Mouse sepsis model (S. aureus B9, p.o.)**	**ED50 [mg/kg] (CI95%)**		**8.72** (6.56-11.67)	**16.62** (11.79-24.19)
Example			**1 in US 7,169,804**	**50 and 58 in US RE39,128**
				
In vitro				
Species		**Strain**	VBV 292	
Staphylococcus aureus	ATCC 10390	B6	0.05	0.1
Staphylococcus aureus	ATCC 29213	B7	0.05	0.1
Staphylococcus aureus	ATCC 29506	B8	0.05	not determined
Staphylococcus aureus	ATCC 49951	B9	0.05	0.05
Staphylococcus aureus	ATCC 9144	B10	0.05	not determined
In vitro Hepatotoxicity human Hepatocytes	**IC50 [µg/ml]**		**83**	**not determined**
In vivo				
***In vivo* Mouse sepsis model (S. aureus B9, p.o.)**	**ED50 [mg/kg] (CI95%)**		**8.83** (5.70-12.88)	**26.71** (15.77-50.30)

Materials and Methods

MIC determination: The minimum inhibitory concentration (MIC) was determined in accordance with NCCLS recommendations by standard agar dilution technique using Mueller-Hinton agar. For MRSA the medium was supplemented with 2% NaCl. The inoculum was 10^4 CFU per spot and inoculation was performed by using a multipoint inoculator (Dynatech, MIC-2000).

Mouse Sepsis Model
New pleuromutilin derivatives were initially evaluated for their *in vivo* antibacterial activity in a septicemia infection model in mice. Methicillin-sensitive *Staphylococcus aureus* (MSSA) B9, originally derived from strain ATCC 49951 was used as infectious agent.
MSSA strain B9 was grown 16 h at 36°C in Mueller-Hinton broth. The final inoculum was prepared by dilution of the bacterial culture with saline to obtain 2.3 x 10^7 CFU in 0.3 ml for intraperitoneal infection of NMRI mice (8 animals/group). The final inoculum given represented a 100% lethal concentration for systemic infections.
Oral antibiotic treatment was performed at several 2- or 3-fold serial doses 1 h and 4 h post challenge.
Mice were observed for a period of 8 days following infection and the mortality was recorded daily. The dose required for survival of 50% of mice at 96 h post infection (ED_{50}) and 95% confidence limits were determined by the binary probit analysis using SYSTAT Version 9.01 (SPSS Inc.). The ED_{50} values refer to the dose given per administration.

In Vitro Toxicity on Primary Human Hepatocytes
Human hepatocytes (10^6 cells/ml; In Vitro Technologies, USA) were incubated with 200, 100, 50, and 25 µg/ml of the test compounds in Krebs-Henseleit bicarbonate buffer (KHB) supplemented with amikacin sulfate (84 µg/ml), calcium chloride (1 mM), HEPES (20 mM), gentamycin sulfate (84 µg/ml), heptanoic acid (4.2 µM) and sodium bicarbonate (2.2 g/l) at 37 °C, 5% CO_2. After 2 hours of incubation cells were lysed and luciferin and luciferase added (ATPLiteTM-Kit, PerkinElmer). Luminescence was measured and compared to the KHB control to determine the percentage of viability. IC_{50} values were calculated using a logistic curve fitting model (Origin 7).